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Hybrid Phosphorus-viologen-dendrimers as new soft nanoparticles. Design and properties.

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Various dendritic structures were prepared during the last decades and their properties emphasized in a number of reviews. Among these macromolecular structures, those incorporating phosphorus units – phosphorus dendrimers – or viologen linkages – viologen dendrimers – stand as the most promising in different fields spanning from chemistry, material science to biology and nanomedicine. The association of the two complementary phosphorus and viologen structures resulted in a nascent family of structures referred as “mixed” hybrid phosphorus-viologen- dendrimers. In light of their specific properties, it was of interest to illustrate the conceptual preparation of a variety of sophisticated hybrid viologen–phosphorus dendrimers including classical dendrimers but also other kinds of mix macromolecules as macromolecular asterisks, onion peel structures and covalent polydendrimer frameworks. Some preliminary results concerning the biological properties of these nano-objects as well as their use for the construction of organic-inorganic hybrid materials are presented.

Introduction

Dendrimers are a class of tailored at will well-defined monodisperse nanostructured macromolecules with diversely multifunctionalized surface. Their size, shape, the nature of the core, the internal branches and the peripheral groups offer the possibilities to use these nano-objects for a great variety of applications ranging from material science, sensing and catalysis, healthcare and biomedical applications.

Among the variety of dendrimers, those incorporating phosphorus at different positions within the structure (core, branching points, surface) are among the most efficient derivatives in terms of chemical reactivity, properties and applications. Indeed, phosphorus dendrimers can be used for example as nanometric sponges,¹ for the formation of fibres,² nanotubes exclusively formed with multilayers of cationic and anionic phosphorus dendrimers,³ hybrid organic–inorganic materials,^{4–6} hydrogels,⁷ microcapsules,⁸ fluorescent nanodots,^{9,10} etc. They also play an important role in the field of catalysis.^{11–13} Last but not least, they exhibited remarkable properties in biology and nanomedicine. Their role can be highlighted for the formation of biochips,^{14,15} as fluorescent species,¹⁶ anti-prions,¹⁷ anti-HIV,^{18,19} anticancer,^{20–26} in the field of human immunity (proliferation of NK cells first line of our

immune system),²⁷ anti-inflammatory,^{28–31} against Alzheimer and Parkinson diseases,^{32,33} as nanocarriers,³⁴ and for dynamic phototherapy.³⁵ Phosphorus dendrimers bearing two-photon absorption (TPA) chromophores at the core, within the cascade structure and on their surface exhibit remarkably higher one or two photon brightness than the best quantum dots avoiding some drawbacks encountered with the later i.e. blinking, insolubility, and toxicity.^{9,10}

Practically, the structure of the large majority of phosphorus dendrimers is constituted with phosphohydrazino branches as shown in Figure 1, the surface being neutral, cationic or anionic. In light of the fascinating properties of these phosphorus dendrimers and dendrons, it appears of interest to see if incorporation of different building blocks within the cascade structure may afford new dendritic nano-objects with original properties and consequently new applications. For this purpose, efforts were directed to incorporate the so-called viologen (dialkylated 4,4-bipyridine) within the cascade structure of phosphorus dendrimers.

Numerous properties of viologen units in different fields can be emphasized.³⁶ For example, viologen linkages can undergo two successive one electron reversible reductions and act as reducing agents for active metal particles,^{37,38} play an important role in electro-redox chemistry, as switchable ionic liquids,³⁹ as mediators for charge-induced energy transfer in photovoltaic devices,⁴⁰ or as versatile photoactive and electrochromic materials.⁴¹

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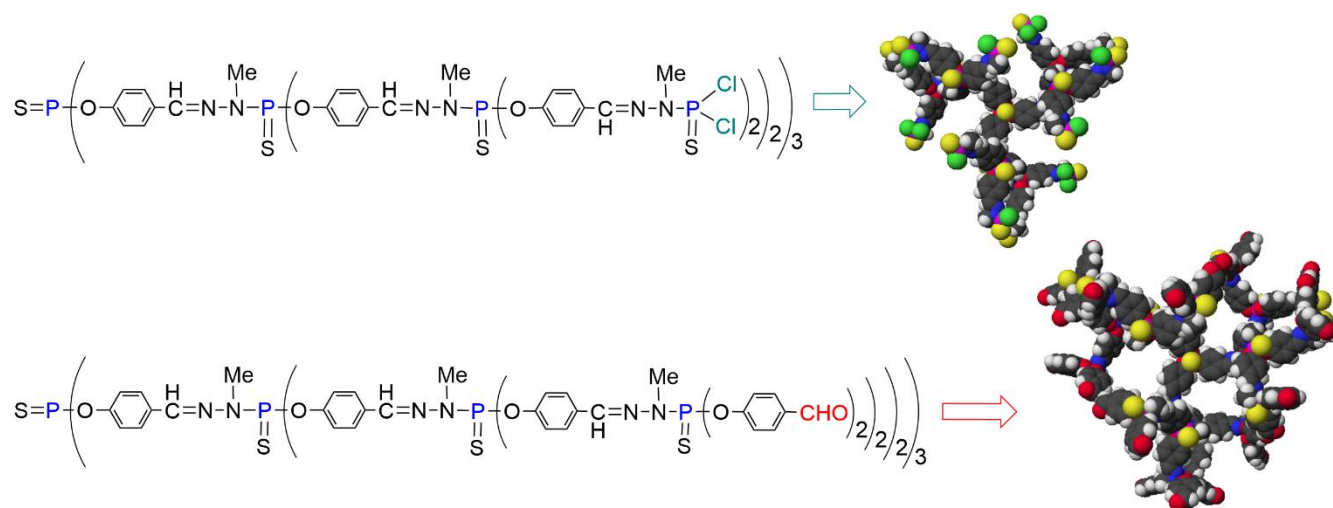


Figure 1. Example of the structure and molecular modelling of neutral phosphorus dendrimers of generation 3 with P(S)Cl₂ (yellow bowl) or aldehyde (red bowl) end groups.

K. Murugavel nicely reviewed the synthesis, properties and applications of viologen dendrimers with emphasis on their electron sponge or charge trapping behaviours, and some aspects concerning their antibacterial, antifungal, antiviral activities or their uses as vectors for nucleic acid delivery.⁴² In the field of nanomedicine, S. Asaftei and E. De Clercq investigated the antiviral activity of a series of viologen dendrimers bearing up to 90 charges against several viruses as for example the Human Immunodeficiency Virus (HIV) and to a lesser extend against other viruses such as the Respiratory Syncytial Virus (RSV), the Herpes Simplex Virus or the Reovirus (RV). The activity was found very dependent of the structure and shape of the viologen dendrimers, the spheroidal dendrimers being more efficient than the comb-branch dendrimers, the number of charges and the distance with the antiviral activity playing an important role.^{43,44} Taking into account the huge possibilities of applications of phosphorus dendrimers in one hand and the own properties of viologen derivatives on the other hand, a fertile landscape in research emanates from mixing these complementary structure in a single building-block. Indeed, this well-timed review aim at illustrating the rational-design of mixed phosphorus-viologen dendrimers and to shed light on the potential use of these novel structures. Investigations were focused on the formation and properties of hybrid phosphorus-viologen dendrimers and new soft nanoparticles constituted with phosphorus and viologen as bricks leading to the design of new families of dendrimers: hybrid organic-inorganic nanoparticles, macromolecular asterisks, onion peel dendritic structures, Janus dendrimers, covalent polydendrimer frameworks, etc.

This review reports the synthesis of new symmetric or asymmetric viologen monomers, dimers, and trimers, the state of the art concerning their use for the construction of new phosphorus dendrons and dendrimers of different generations or mixed phosphorus carbosilane viologen dendrimers and dendrons. Some of their biological properties and their use for the formation of original nanomaterials are also presented.

Synthesis of phosphorus–viologen structures

Synthesis of hybrid phosphorus–viologen dendrimers

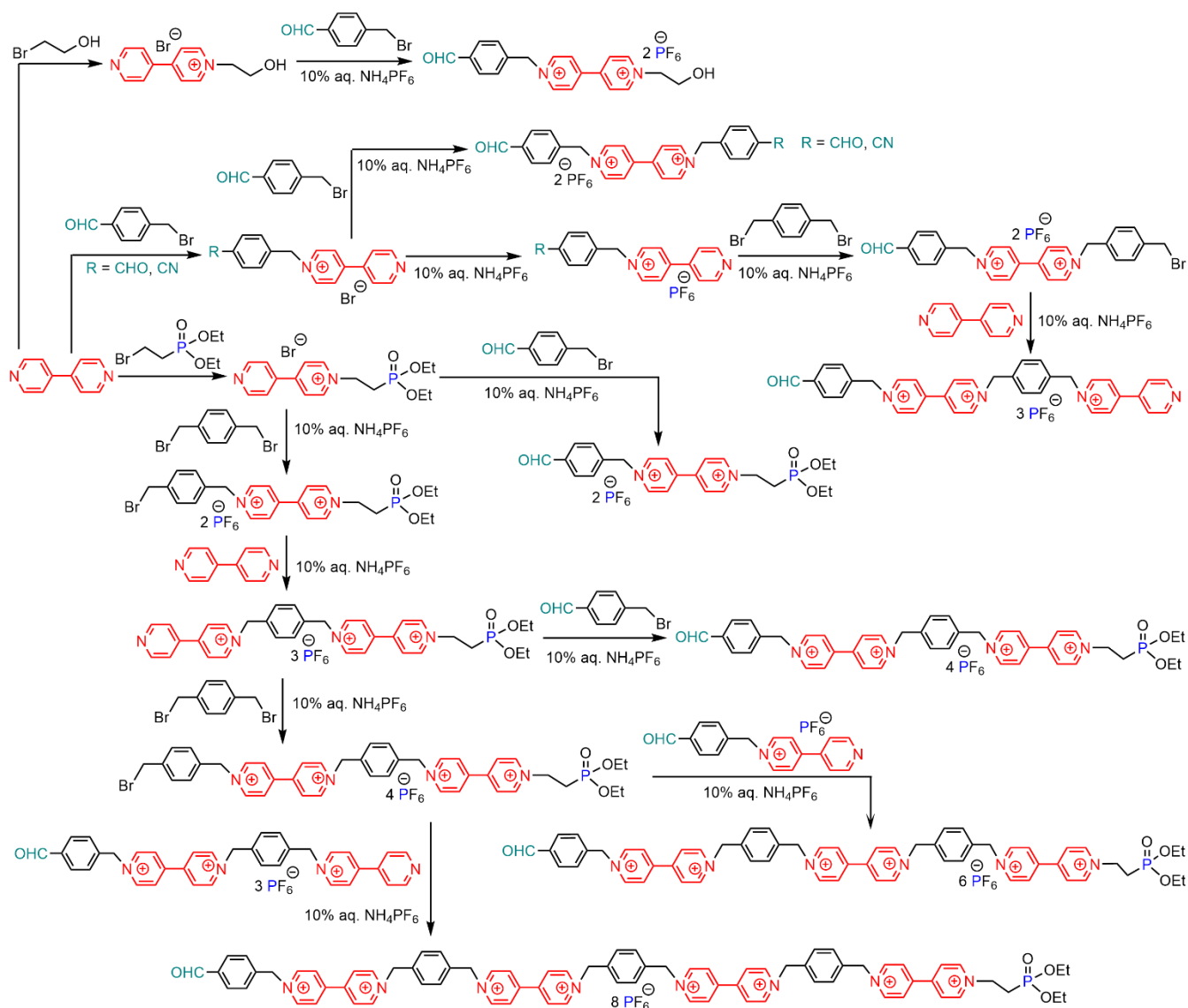
A combination of successive highly efficient and versatile chemical reactions allows the preparation of a variety of mono-, bis- and tetrakis viologen-based molecular and macromolecular building blocks as shown in Scheme 1. These viologens bearing an aldehyde group were the starting units for the synthesis of phosphorus viologen dendritic structures: condensation reaction with either (S)P[NMeNH₂]₃ or P₃N₃[NMeNH₂]₆ used as core allows to graft up to 18 viologen linkages and up to 36 positive charges at different levels within the cascade structure and on the surface of the final compounds (Scheme 2, Figure 2).⁴⁵

Macromolecular asterisks

An interesting approach to the design of original amphiphilic viologen-based dendritic macromolecules asterisks incorporating three types of phosphorus units namely a cyclotriphosphazene core, phosphonates as terminal groups and hexafluorophosphate as counter anions was proposed from the reaction of hexahydrazinocyclotriphosphazene used as a core with various mono-, bis-, tris- and tetrakis-viologen-based molecular and macromolecular building blocks terminated with aldehyde groups (Scheme 3). A series of linear asterisks incorporating up to 24 viologens were prepared. An hypochromic effect in UV-visible spectroscopy was observed when moving from the monomeric viologen to the asterisk forms probably due to the difference in the supramolecular organisation of these macromolecules. The interaction of these viologen phosphorus macromolecular asterisks with HAuCl₄ was investigated and several interesting phenomena can be pointed out: 1/ exchange of anion with the formation of viologen⁺-AuCl₄⁻, 2/ formation of isotropic gold nanoparticles (without any presence of bulky aggregates) entrapped within the asterisk structure upon addition of NaBH₄ with apparition of a broad surface

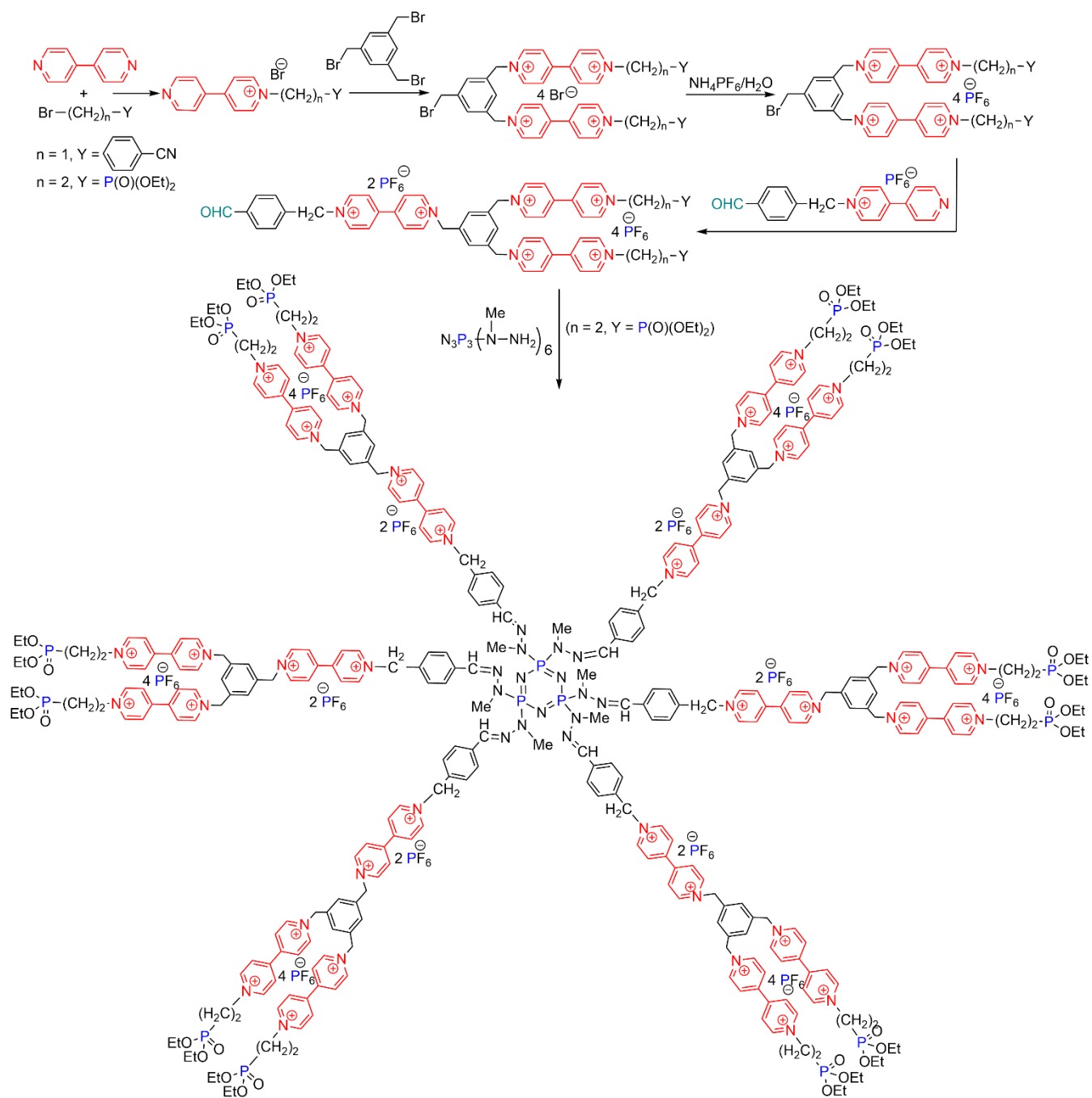
plasmon resonance band centered at 523-535nm, the size of these gold nanoparticles varying from 7 to 45 nm, the smaller asterisk being the least efficient to control and limit the growth of the asterisk

gold nano-objects (Table 1); 3/ the remarkable stability for up to eight months of such metallic macromolecular asterisks.⁴⁶

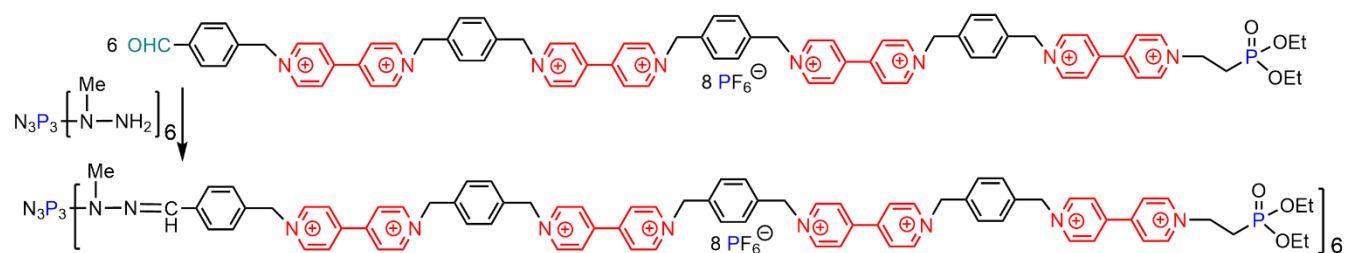


Scheme 1. Synthesis of mono, bis- and tetrakis viologen-based molecular and macromolecular building blocks.

REVIEW



Scheme 2. Example of synthesis of a hybrid phosphorus viologen-dendrimer.



Scheme 3. Examples of synthesis of macromolecular phosphorus-viologen asterisks.

REVIEW

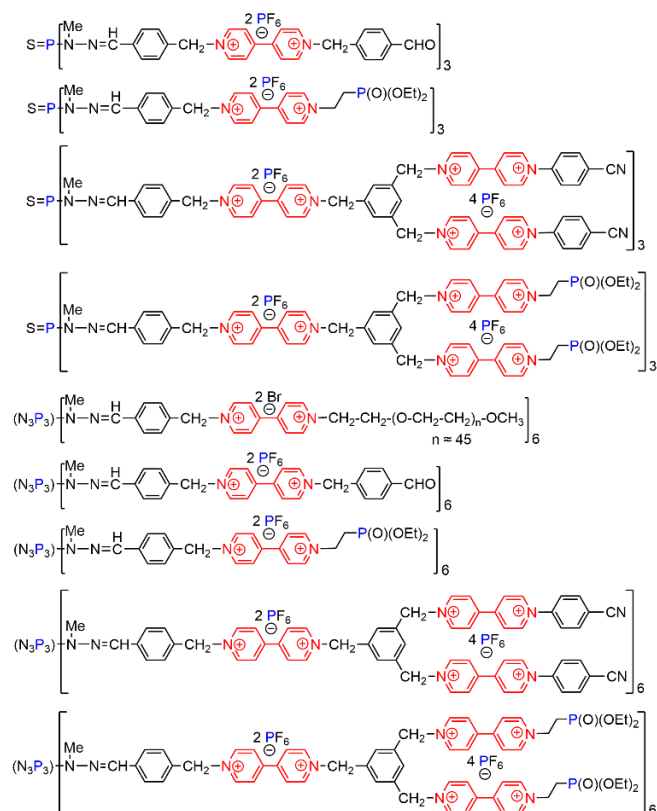


Figure 2. Some examples of phosphorus-viologen dendrimers prepared either from $S=PCl_3$ or $P_3N_3Cl_6$.

Onion peel dendrimers

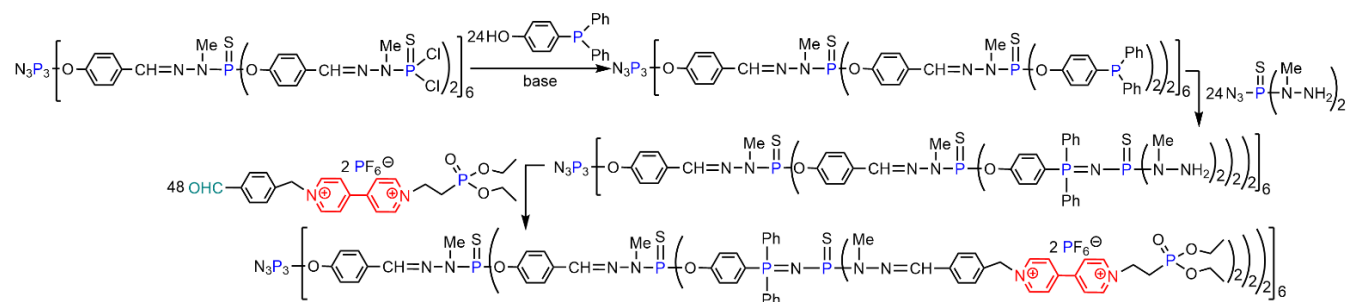
Main Text Paragraph. Efforts were also turned towards the design of « onion peel » nanodendritic phosphorus species in which a large variety of phosphorus units are regioselectively incorporated stepwise, each of them allowing the possibility to increase the functionalities of the final macromolecules. For such a goal, a straightforward Staudinger-type reaction between phosphino end groups and the azide $N_3P(S)(NCH_3NH_2)_2$ afforded dendrimers with terminal hydrazino groups (Scheme 4). Then, the condensation of the peripheral hydrazino groups with viologen bearing aldehyde on one side was carried out.⁴⁷ A library of « onion peel » macromolecules incorporating up to 48 viologen groups located close to the surface, and seven different types of phosphorus units for the higher generation 3 was prepared (Figure 3). Interestingly each layer is different, constituting an unprecedented class of phosphorus macromolecules and polymers. The presence of internal $P=N-P(S)$ linkages allows to selectively incorporate up to 48 Au(I), thus illustrating the possibility to perform regioselective reactions inside the structure of these hybrid macromolecules.⁴⁷

Table 1. UV-Visible and fluorescence data for Viologen⁺-AuCl₄⁻, Viologen@AuNPs, and diameter of gold NPs.

Compound	Viologen ⁺ -AuCl ₄ ⁻ [a]	Viologen@AuNPs [b]	Diameter AuNPs (nm) [c]
D1V		289 (530)	45
D2V		269 (535)	8.5
D3V		293 (523)	7.5
D4V		294 (528)	7

[a] UV-Vis. analysis (nm). [b] UV-Vis. upon addition of NaBH₄ (nm). The value between brackets corresponds to the characteristic band of gold nanoparticles (nm). [c] average particle size measured using HRTEM.

REVIEW



Scheme 4. Synthesis of onion peel dendrimers.

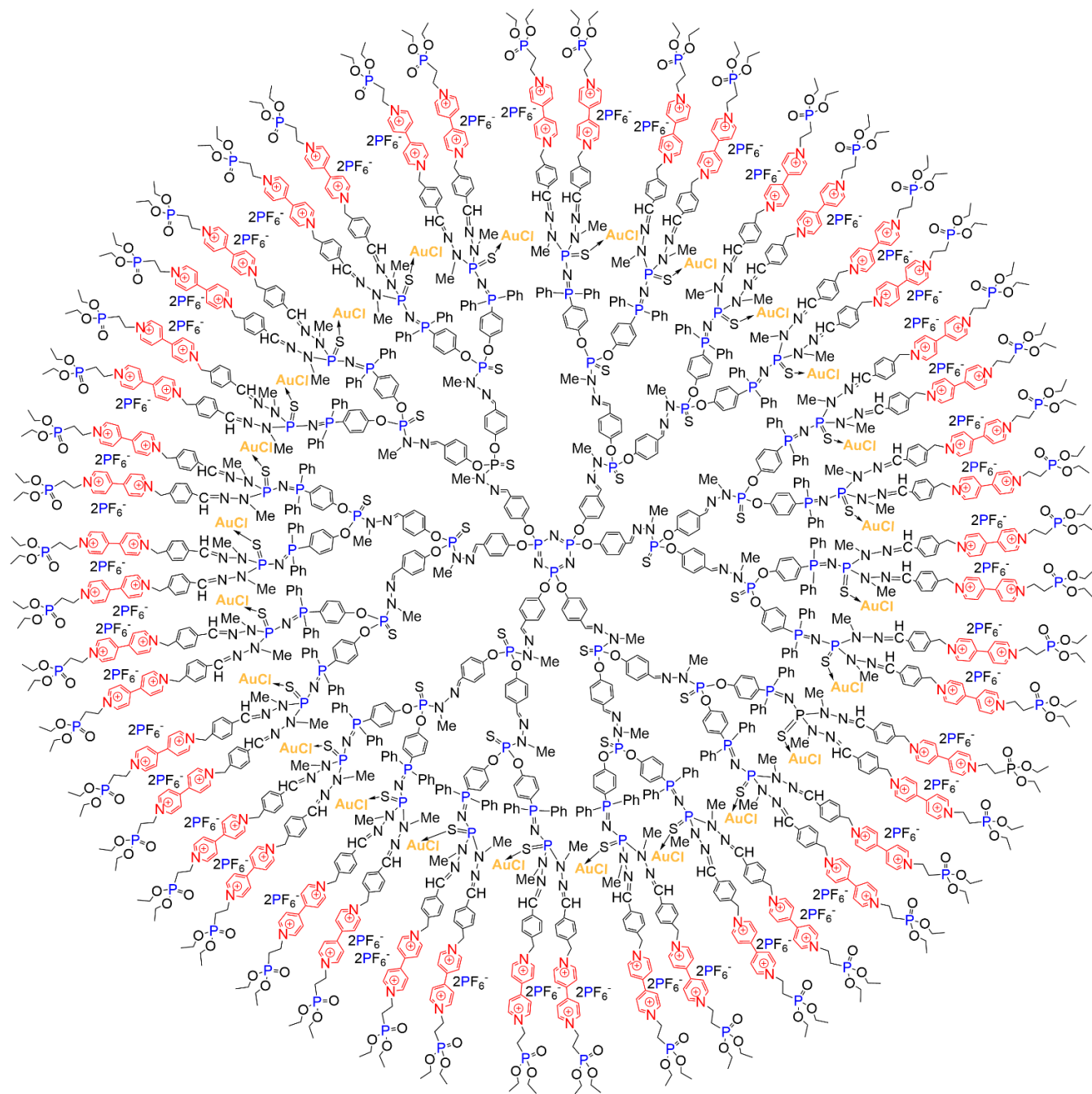


Figure 3. Full structure of an onion peel dendrimer.

Later on, other families of onion peel dendritic structures were designed from two different building blocks: the hexahydrazino cyclotriphosphazene as a core and double functionalized carbosilane dendrons. The latter was prepared by two subsequent quaternization steps on bipyridine ligand, leading to hybrid systems with therefore a phosphorus core, 6, 12 or 24 viologens as branches and 6 carbosilane wedges of generation 1 (**SMT1**) or 2 (**SMT2**) (Figure 4).⁴⁸ Interestingly, these hybrid

dendritic derivatives possess different types of positive charges along their structures, within the branches for the viologens and on the surface decorated with ammonium groups. Consequently, these mixed onion peels are easily soluble in aqueous medium and can be used in water-based application, thereby offering another channel of possibilities for green and bio-based chemistry.

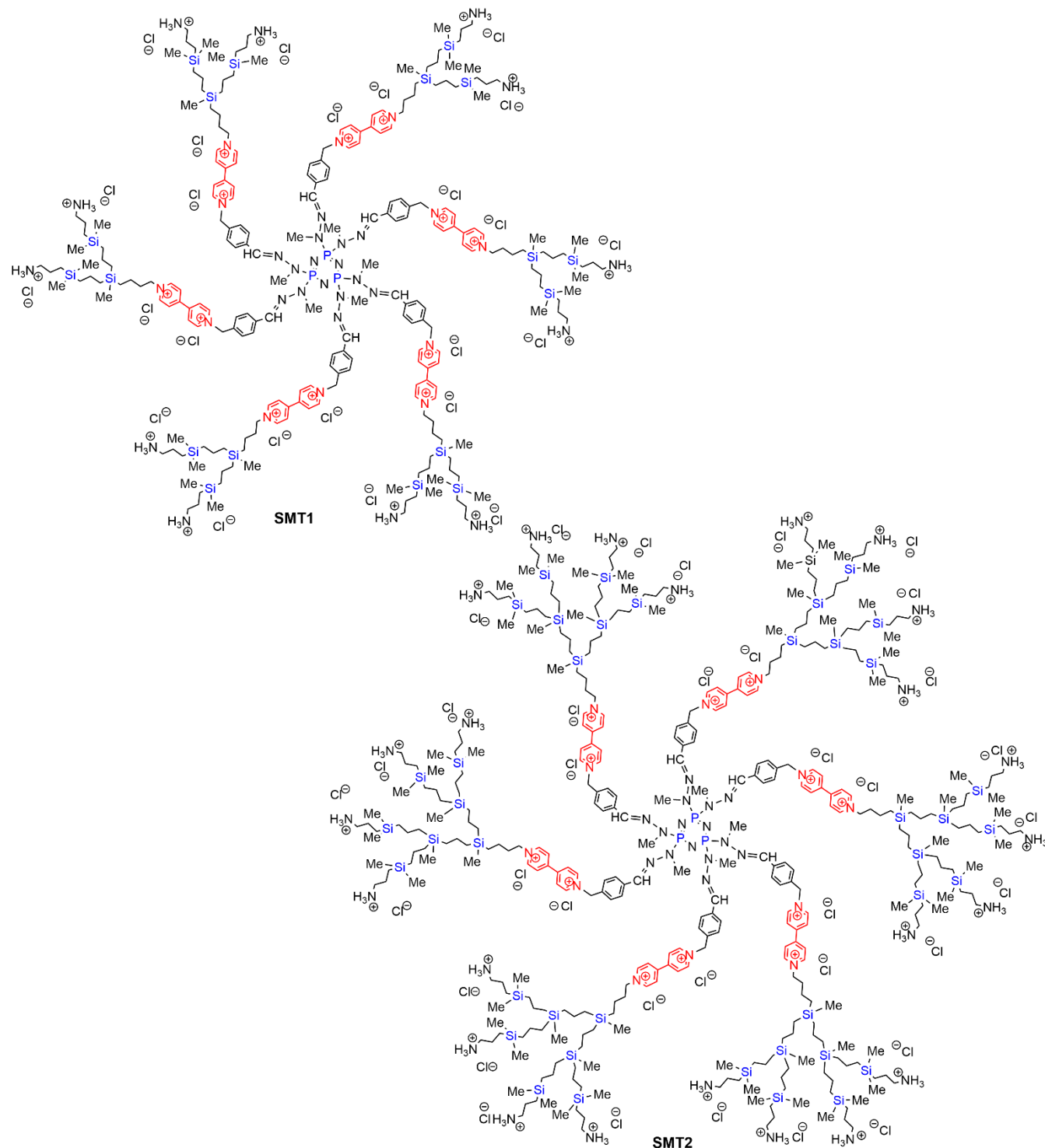
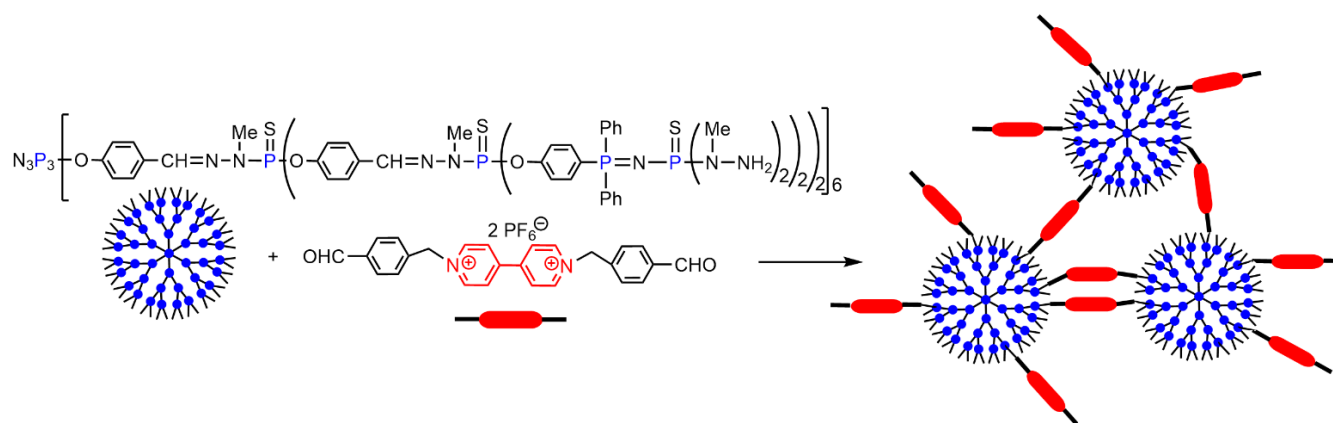


Figure 4. Full structure of hybrid dendrimers of generation 1 (**SMT1**) and 2 (**SMT2**).



Scheme 6. Example of synthesis of original polydendrimers.

Covalent polydendritic frameworks

Another example of polymerisation concerned the co-condensation of phosphorus dendrimers bearing either terminal aldehyde, carboxylic or hydrazino groups that led to a variety of new dendritic polymeric macromolecules. The methodology uses phosphorus dendrimers as building blocks that could be connected through classical reactions including aldehyde-hydrazine Schiff base formation, or amine-to carboxylic acid peptide like coupling.⁶³ A library of original polydendrimers was established playing with the size of each individual phosphorus dendrimer partner (generation 1-3) and the number of their functional end groups. Scanning electronic microscopy revealed the presence of homogeneously shaped nanospheres ranging from 100 to 300 nm witnessing on regular and controlled polymerisation, while transmission electronic microscopy provided a clear picture of the organisation at the nanoscale. Interestingly, reticulation of phosphorus dendrimers of various generations with a rigid benzyl-viologen terminated dialdehyde affords new created material networks of hyperbranched polymer-like architectures with intervoid porosity and slight nanoscale ordering (Scheme 6).⁶³

Biological properties of phosphorus-viologen structures

The investigation of interaction of newly synthesized hybrid dendrimers with biological structures is an important part of studies of their toxicity, bioavailability and efficiency. These tests can be divided into three main groups: 1) studying the interaction between a new structure with supramolecular biomolecules such as lipid bilayers, proteins, nucleic acids, 2) studying toxicity and efficiency of these structures in vitro, 3) in vivo researches. All of them are the necessary steps for detailed analysis of toxicity and efficiency of these mixed macromolecular species.

Interaction of Phosphorus-viologen dendrimers with lipid bilayer

Ciepluch et al.⁶⁴ found that the interactions between the cationic-phosphorus-viologen dendrimer, hyperbranched polyethylenimine (PEI) modified by maltose and negatively charged lipid membranes are due to attractive electrostatic interactions. The interaction between probe moieties and lipid bilayers and the level of disruption

of this bilayer depended on size, shape, and structure of the dendrimers (Figure 5).

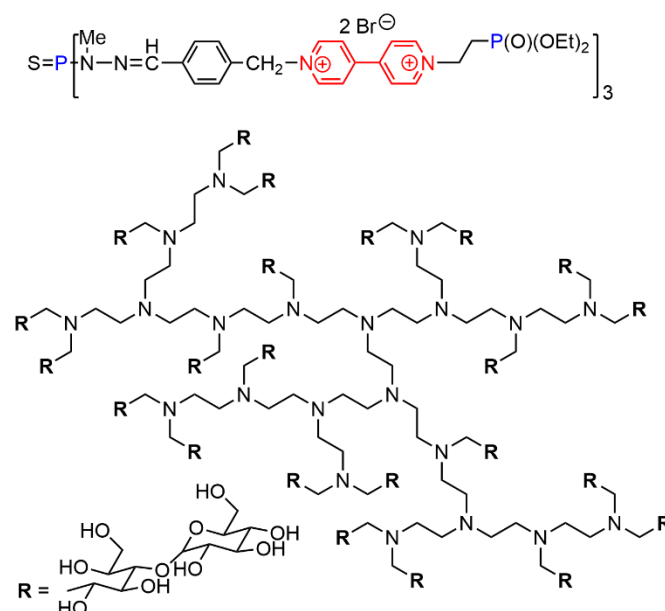


Figure 5. Cationic phosphorus-viologen dendrimer, and hyperbranched PEI modified by maltose.

Interaction of Phosphorus-viologen dendrimers with proteins

The basic principles of interaction between a series of phosphorus-viologen dendrimers (Figure 6) and proteins were studied by Ciepluch et al.⁶⁵ on the example of human serum albumin (HSA) illustrating the important and versatile role of different structural parameters of the viologen phosphorus dendrimers: 1/ the dendrimers **4**, **5** (higher molecular mass, higher number of viologen linkages, terminal phosphonate groups) significantly quenched the fluorescence of HSA thus indicating a collisional mechanism of quenching but have no effect on the free tryptophan fluorescence and no influence on the CD spectra of albumin. 2/ In contrast the viologen phosphorus dendrimers **1** and **2**, as well as the viologen **3** bearing aldehyde end groups quenched both free tryptophan and HSA fluorescence and also changed the secondary structure of albumin.⁶⁵

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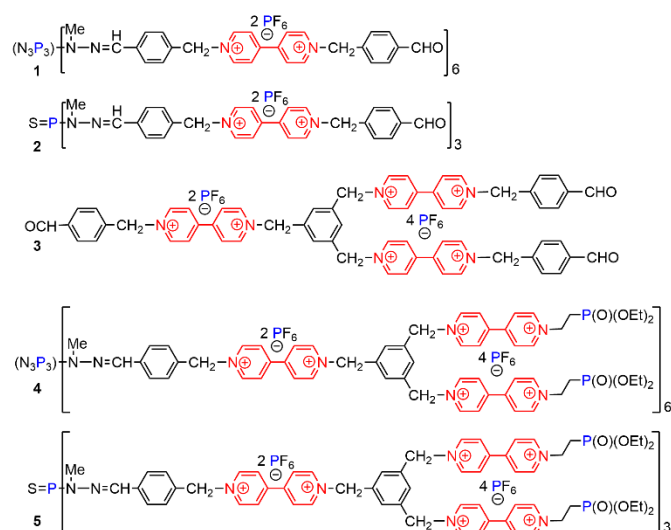


Figure 6. Viologen phosphorus dendrimers used for studying their interaction with human serum albumin (HSA).

Phosphorus-viologen dendrimers and hybrid carbosilane–viologen–phosphorus dendrimers interacted with human serum albumin by, preferentially, electrostatic forces. But, differences in interaction with HSA were observed for both of them. These effects were explained by the differences in the size and surface charge of both dendrimers.⁶⁶

The effect of a phosphorus -viologen dendrimer of generation 0, compound **6** (Figure 7) as well that of monomeric viologens bearing from two to six aldehyde groups on acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) was investigated both of these enzymes being involved in neurodegenerative diseases. It was found that all the different viologen compounds inhibit the activities of both cholinesterases, via the binding to either a peripheral site of the enzyme or to amino acids located near the active site.^[67] In the same vein and with the objective to evaluate the possible biological properties of different types of phosphorus viologen dendrimers Szwed et al.⁶⁸ compared the ability of interaction between 2 hybrid carbosilane-viologen-phosphorus dendrimers of generation 1 and 2 (see Figure 4) with 3 regulatory proteins: alkaline phosphatase from *E. coli*, human aspartate transaminase and L-lactate dehydrogenase from rabbit muscles. As expected, complexes were formed via electrostatic forces with a strong quenching of the fluorescence of the three proteins, the formation and the nature of these complexes depending mainly of the special configuration of the dendrimers and of the proteins.

Inhibition of α -synuclein fibril formation is a potential therapeutic strategy in Parkinson's disease and other synucleinopathies. Milowska et al.^[69-71] analysed the role of two viologen-phosphorus dendrimers of generation 0, each of them having the same core, both bearing 12 positive charges, the nature of the terminal groups being different, phosphonate units for the dendrimer **7** and PEG groups for the dendrimer **8**, on the α -synuclein fibrillation process and on the structural changes in α -synuclein. (Figure 7) In all cases, α -synuclein fibrillation kinetics can be significantly reduced, and even, totally inhibited in the case of the dendrimer bearing phosphonate end

groups (**7**) at low concentration, thus opening the possibility to use it as fibrillar regulating agent in neurodegenerative disorders.

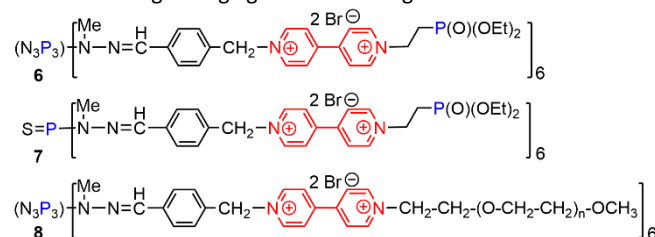


Figure 7. Viologen phosphorus dendrimers used for studying their interaction with enzymes, and on α -synuclein fibril formation.

Interaction of Phosphorus-viologen dendrimers with cells in vitro

Lazniewska et al. examined the impact of 3 viologen phosphorus dendrimers (Figure 7) on the murine neuroblastoma cancer cell line (N2a)⁷² and on murine hippocampal cell line (mHippoE-18).⁵⁹ For such an investigation several techniques were used as cytotoxicity test, reactive oxygen species generation studies, mitochondrial membrane potential assay, cell death detection, cell morphology assessment, cell cycle studies, as well as measurements of catalase activity and glutathione level. A slight toxicity was found, structure of VDP **7** being the least toxic one. However, the dendrimers did not cause a strong cellular response, induced a low level of apoptosis and have ability to quench ROS making the nanodevices possible candidates to be used as drug *per se*.^[72-73] Moreno et al.^[66] found differences in cell viability of hybrid carbosilane–viologen–phosphorus dendrimers **SMT1**, **SMT2** (Figure 4) versus viologen phosphorus dendrimers for Chinese hamster fibroblasts (B14 cell line). They suggested that toxicity was related to the outer positive charges, with significant effect caused by the internal ones. However, respecting hemotoxicity, no correlation due to the number of outer positive charges was observed.⁴⁷

Antimicrobial and antifungal activity of phosphorus-viologen dendrimers

Ciepluch et al.⁷⁴ focused their experiments on hemotoxicity, erythrocyte morphology, membrane fluidity, in vitro cytotoxicity and antibacterial activity of seven viologen phosphorus dendrimers of generation 0 and 1 bearing from 3 to 18 viologen linkages (compounds **1**, **2**, **4**, **5** Figure 6, compounds **6**, **7**, **8** Figure 7) and one building block incorporating 3 viologen groups and used for the construction of some of these dendrimers (compound **3**, Figure 6). Dendrimers bearing the highest number of charges, i.e. the highest number of viologen units, present the strongest hemolytic effect and interact more efficiently with membranes. Interestingly among these 8 dendrimers incorporating viologen units two of them, compound **7** and the PEGylated dendrimer **8**, are not toxic to B14 cells but are very cytotoxic toward cancerous cells N2a. It is known that the chemical structure, surface charge, 3D structure and size play a crucial role in determining antimicrobial activity. All tested dendrimers exhibited good antimicrobial properties toward the Gram-positive strain *S. aureus*. Dendrimers **4** and **5** (Figure 6), which bear the highest number of viologen units and consequently the higher number of positive charges also limited the growth of Gram-negative strains *E. coli* and *P. vulgaris*.⁷⁴

Phosphorus-viologen dendrimers can bind nucleoside analogues

Szulc et al.⁷⁵ studied the interactions between the dendrimer **7** of generation 0 bearing 3 viologens and 3 phosphonate groups with the negatively charged nucleotides ATP and 20-/30-O-(N-methylanthraniloyl)-ATP (Mant-ATP, considered as model molecules of purine and pyrimidine nucleoside analogues, antimetabolites commonly used in anticancer therapy (Figure 8). Stable complexes of **7** with nucleoside analogues may help to overcome severe limitations of nucleoside analogues associated with their low solubility, stability or resistance to cancer cells. Compound **7** forms stable complexes with ATP and Mant-ATP with high efficiency, these complexes being stabilized by electrostatic and aromatic–aromatic interactions as driving forces. In fact, the formation of these complexes is dependent of diverse factors as the pH, the polarity of the environment, the solvent. Anyway, these results open the way to use this dendrimer as carrier of nucleoside analogues such as anticancer drug fludarabine.⁷⁵

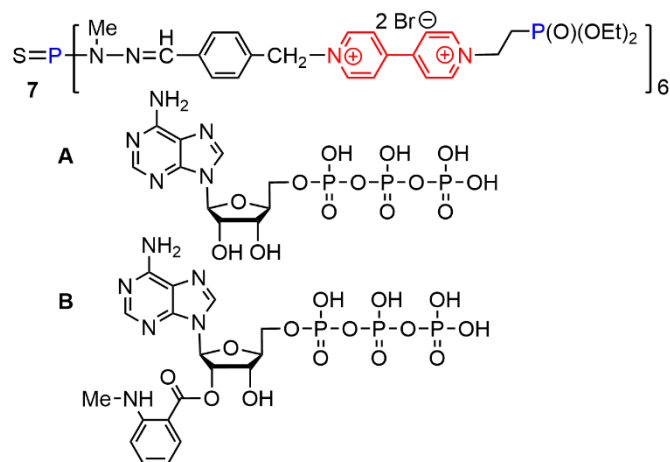


Figure 8. Chemical structures and hydrogen labeling in the viologen phosphorus dendrimer (**7**), ATP (**A**) and a chemical structure of Mant-ATP (**B**).

Hybrid carbosilane-viologen-phosphorus dendrimers can enter mitochondria

Szved et al.⁷⁶ examined the carbosilane–viologen–phosphorus dendrimers (**SMT1** and **SMT2**, see Figure 4) effects on the basic cellular processes of nerve cells: cancer cell line N2a (mouse neuroblastoma) and normal immortalized cell line mHippoE-18 (embryonic mouse hippocampal cell line). Interestingly, these dendrimers are more toxic on these cancer cell lines than on normal cell lines at low concentrations. Moreover, the highest generation induced greater cytotoxic effects and morphological modifications. The most promising is the dendrimer **SMT1** which can reach mitochondria. To summarize these two hybrid carbosilane-viologen-phosphorus dendrimers, **SMT1** and **SMT2** can be considered as possible nanocarriers to mitochondria and offer the possibility to be used as anti-cancer drugs *per se* in CNS disorders.⁷⁶

Phosphorus-viologen dendrimers can protect cells from damage

Rotenone is an isoflavone acting as a damaging agent associated to Parkinson's disease, and also used as pesticide and insecticide. Milowska et al.⁷⁷ analysed the interesting features of various dendrimers as PAMAM (generation 3 and 4), polycationic phosphorus dendrimers of generation 3 and 4 and the viologen

phosphorus dendrimer **6** (Figure 9) whether they can prevent damage to embryonic mouse hippocampal cells (mHippoE-18) caused by rotenone. mHippoE-18 cells were treated with dendrimers including the viologen phosphorus dendrimer **6** (0.1 mM) and with rotenone at 1 mM. It was found that all these dendrimers including the viologen phosphorus dendrimer **6** increased cell viability with a favourable effect on the mitochondrial system and lower level of reactive oxygen.

Conclusions and perspectives

During several decades, researchers were mainly interested to design various types of dendrimers starting with a given core and developing the structure of the dendrimers via the reiteration of reactions involving the same building blocks at each generation. This was the case for the formation of a variety of dendrimers like PAMAM, PPI, polylysine dendrimers, carbosilanes, viologen or phosphorus dendrimers to name a few. Properties and applications were also successfully investigated in numerous fields as catalysis, nanomaterials, biology, nanomedicine etc. More recently, interest was focused on the design and applications of “mix dendrimers” that is to say dendrimers constituted with two or more different layers with the hope to discover new applications or at least to increase the possibilities of applications of these new soft hybrid nanoparticles in different fields. This trend is illustrated by the synthesis of a variety of original viologen phosphorus with a large molecular diversity and different secondary-structures, including dendrimers, dendrons, onion peel structures, macromolecular asterisks etc. Such investigation enabled diversification of the library of dendrimers. These easy-to-run reactions triggered later substantial research focusing on the properties of the resulting nano-objects.

In the field of nanomaterials, focus can be done on the trapping of gold nanoparticles generated *in situ* within the cascade structure of the dendrimers with the formation of unprecedented metallic macromolecular asterisks, the entrapped gold nanoparticles being stable for up to eight months. Last, new nanomaterials based on the association of dendrimers of different generations with a viologen monomer ended with aldehyde units led to the formation of new material networks of hyperbranched polymer-like architectures with intervoid porosity and slight nanoscale ordering. Such preliminary results open the way for the formation of different mix networks constituted by different dendritic units which might possess interesting properties as nanomaterials.

As it was expected and mainly illustrated by K. Muragavel, the toxicity of viologen fragments even when these fragments were incorporated within the dendrimer framework is practically insurmountable for the development of applications in nanomedicine. Anyway, several observations are encouraging: interaction of these hybrid dendrimers with proteins, cells *in vitro*, lipid bilayers, binding nucleoside analogues, protection of some cells from damage, uptake into mitochondria. Antimicrobial and antifungal activities of a variety of viologen phosphorus dendrimers were also illustrated. Remarkably two of these hybrid dendrimers were found for example to be not toxic to B14 cells but very toxic towards cancer cells N2a. Of interest also, some of these dendrimers can prevent damage to embryonic mouse hippocampal cells caused by rotenone, a damaging agent associated to Parkinson disease.

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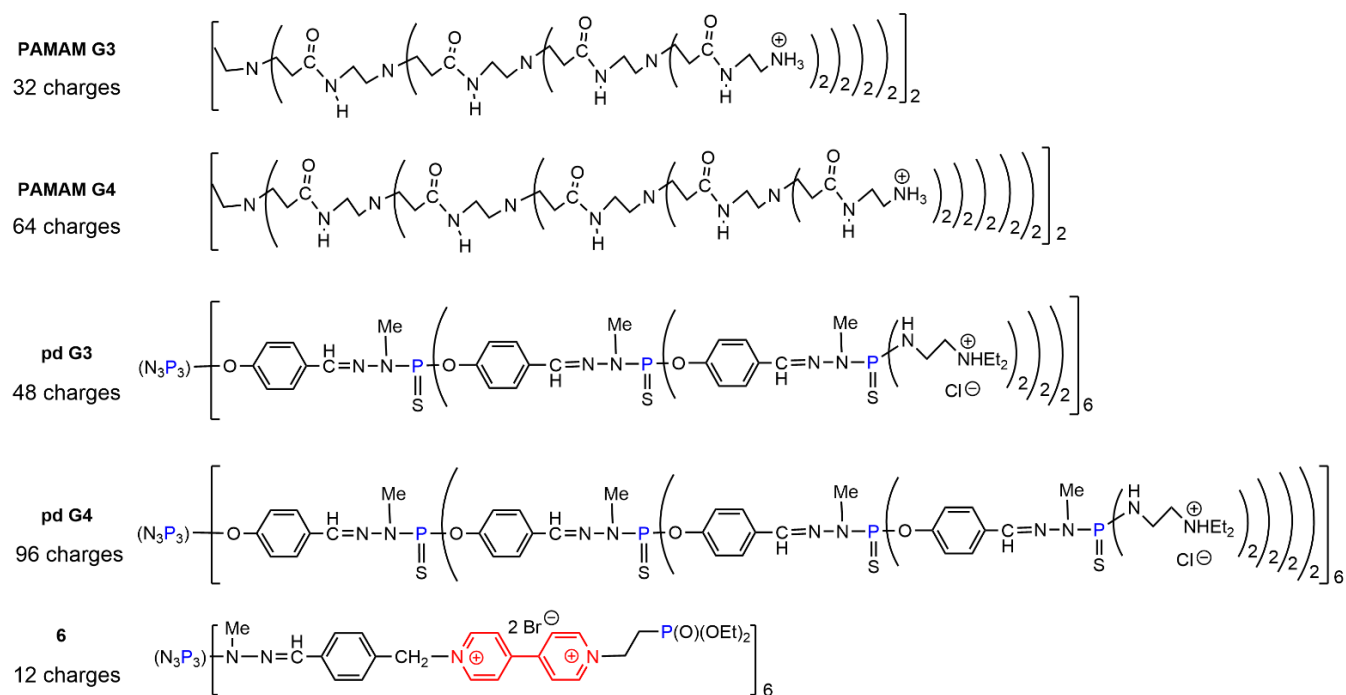


Figure 9. Structures of dendrimers used for studying rotenone-induced damage of cells.

Author Contributions

J.P.M.,D.S, M.B, A.EK conceptualisation and investigation; M.Z, N.K.,K. C., K. M.methodology; J.P. M supervision, A.M.C. visualisation,,J.P. M.,A.E.K,D.S. writing original draft, J.P. M.S.M.,writing-review editing

Conflicts of interest

There are no conflicts to declare.

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REVIEW

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